IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No: 20780-0006

Applicant(s):	Jeffrey W. RUBERTI et al.	Confirmation No.: 9743
App. No.:	10/771,852	Examiner: K. C. Egwim
Filing Date:	February 4, 2004	Group Art Unit: 1713
Title:	SYSTEMS AND METHODS FOR CONTROLLING AND FORMING POLYMER GELS	

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DECLARATION OF STEPHEN SPIEGELBERG

I, Stephen Spiegelberg, do hereby declare as follows:

1. I received my Ph.D. in Chemical Engineering from the Massachusetts Institute of Technology (MIT) in 1993. I have been engaged in the study of polymers, such as vinyl polymers for *in vivo* use over 15 years. I have authored or co-authored at least 50 peer-reviewed papers and presentations, several book chapters and co-invented several US Patents related to polymeric materials and their use in medical prosthetics. I am a co-founder and currently the President of the Cambridge Polymer Group, Inc.

2. I understand that the claims in the captioned patent application have been rejected allegedly as being anticipated by Hyon (US 4,663,358), Tanihara (US 5,880,216), Ku (US 5,981,826), Yao (US 6,268,405), Yamauchi (JP 03215417), or Okamura (JP 04338326); or in the alternative, as being obvious over Tanihara (US 5,880,216), Ku (US 5,981,826), Yao (US 6,268,405), or Okamura (JP 04338326).

The examiner has noted in the Office Action issued November 2, 2006, that the applicants provide insufficient evidence to support the conclusionary statements that the "[f]reeze-thaw process does not permit preparation of an injectable formulation" and

"[the] Hyon method can not yield an injectable hydrogel." Apparently the examiner has invited the applicants to provide evidences to prove so.

The examiner also specifically referred to Yao *et al.*, col. 9, lines 58-67, and believed that depending on the end use, the hydrogel can be repeatedly freeze-thawed to increase it's viscosity and, after one cycle, the hydrogel would still be at least injectable.

In order to address the issue and to demonstrate that the none of the processes disclosed in the cited references would yield "injectable hydrogel", I submit the following:

3. The experiments outline below are intended to demonstrate that: the hydrogel produced by freeze-thaw treatment, even after one cycle, would not be injectable.

Example 1. Can a Hydrogel Produced by One Cycle of Freeze-thaw Treatment be Injectable?

Materials prepared: One Freeze-thaw cycle PVA hydrogel was made from 15 wt% PVA in deionized (DI) water by freezing for 8 hours and then thawing for 4 hours. Materials used were equilibrated in DI water for 4.5 years (manufactured on August 13, 2002).

The PVA hydrogel sample produced by the single freeze-thaw cycle was placed on a 4 mm (#22 drill ~ 9G needle) orifice on a flat plate and loaded using a second flat plate and a mass. Mass used was 4.99 kg (11 lbs). With up to a 5.75 mm orifice, and 4.99 kg mass, there was no evidence of flow through the hole, or extrusion or expulsion (See Figures 1-9). For reference, the usual injection pressure employed by anesthesiologists is ~25 psi (see Claudio *et al.*, Regional anesthesia and Pain Medicine (2004) 29(3) pp 201-205 (abstract), copy attached), which is 172 kPa or 450 g of load for the 5.75 mm orifice. Since the sample is only free to move at the orifice the effective pressure on the sample is only across the orifice diameter of 5.75 mm, which results in a pressure of 1.9 MPa (275 psi), well in excess of the nominal injection force.

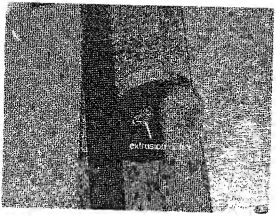

Figure 1: Shows a setup of a polycarbonate sheet with a drilled 4 mm hole. The sheet is suspended in order to allow camera access from the bottom.

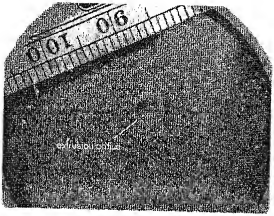

Figure 2: Shows that the 4 mm hole in the polycarbonate sheet is clearly visible through the bottom of the sheet.

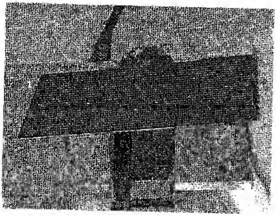

Figure 3: Shows that the sample is placed on the polycarbonate sheet containing the 4 mm hole and a thin metal sheet is placed on top (with no load) to protect sample.

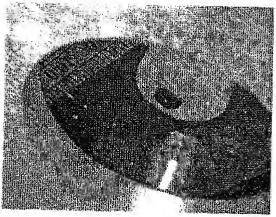

Figure 5: Depicts the same setup as in Figure 4 at an oblique angle (4 mm hole, with no load).

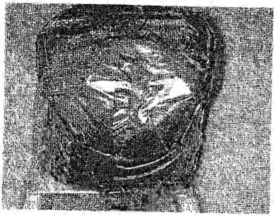

Figure 6: Shows that a mass of 4.99 kg (~11 lbs) is placed on top of the metal sheet and the sample is weighted down.

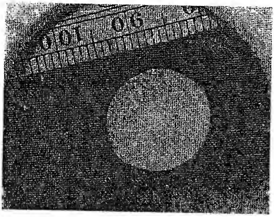

Figure 4: Shows that the thin metal sheet alone as the load, the sample is barely compressed or deformed (on the 4 mm hole without the load).

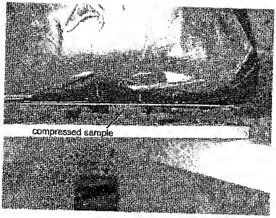

Figure 7: Demonstrates clearly that the sample is compressed heavily under the applied load of 4.99 kg on the 4 mm hole.

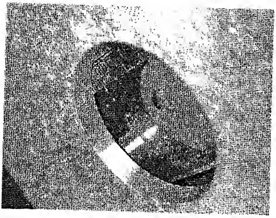

Figure 8: Illustrates an oblique view of 4.99 kg load and 4 mm orifice. No material is ejected under the applied force.

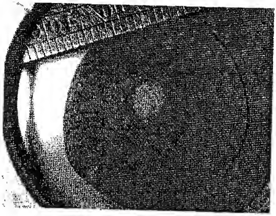

Figure 9: Shows that the Orifice replaced with a 5.75 mm hole (#1 drill, ~5G needle), 4.99 kg load. Again, no material is ejected from the orifice under the load.

Above experiment and the data (Figures 1-9) clearly demonstrate that the hydrogel produced by one cycle freeze-thaw treatment is not injectable.

Example 2. Hydrogel produced by a single cycle freeze-thaw treatment is not injectable.

Materials prepared: One Freeze-thaw cycle PVA hydrogel was made from 15 wt% PVA in deionized water by freezing for 8 hours at -10°C and then thawing for 24 hours at room temperature.

A control sample of 15 wt% PVA in deionized water was prepared, which did not undergo the freeze-thaw treatment.

The hydrogel samples prepared were placed in separate 20 cc syringes.

The syringes were inverted and placed on a scale in order the register the force required to eject the material from the syringe opening, which has a diameter of 1.9 mm.

The control sample was ejected from the syringe opening with an applied force of 8 lbs, corresponding to a pressure of approximately 9.4 psi. This pressure is well within the injection pressure range used clinically (25 psi) (see Figures 10-12).

The hydrogel prepared by the single cycle freeze-thaw process could not be ejected from the syringe, even with an applied pressure of 45 psi at the plunger and a generated pressure of 9,500 psi at the orifice of the syringe (see Figures 13-14).

When removed from the syringe, the hydrogel prepared by the single cycle freeze-thaw process found to be a monolithic elastic sample with good mechanical integrity (see Figure 15). The hydrogel appeared to possess no injectable properties (see Figure 16).

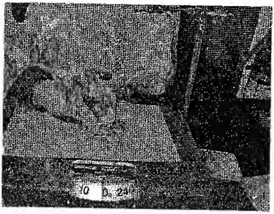

Figure 10: Illustrates the apparatus configuration, showing a 20 cc plastic syringe containing 15 wt% PVA in deionized water. The scale registers the downward force exerted (units of lbs).

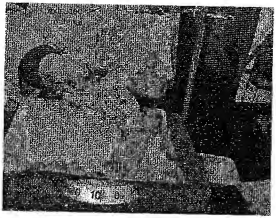

Figure 11: Shows that the 15 wt% PVA in deionized water extrudes from the 20 cc syringe with a force of approximately 8 lbs. This force correlates to approximately 9.4 lbs/in^2 (psi).

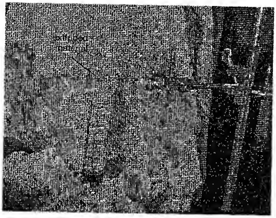

Figure 12: Shows a close-up view that the 15 wt% PVA in deionized water extrudes from the 20 cc syringe with a force of approximately 8 lbs. This force correlates to approximately 9.4 lbs/in^2 (psi).

Figure 13: Demonstrates the injection test with 15 wt% PVA in deionized water that underwent one freeze-thaw cycle. At 38 lbs of force, corresponding to 44.6 lbs/in^2 in the bulk and 9,500 lbs/in^2 at the orifice, no material was extruded.

Figure 14: Shows a close-up view of the syringe orifice during injection test with 15 wt% PVA in deionized water that underwent one freeze-thaw cycle. In image, 38 lbs of force, corresponding to 44.6 lbs/in^2 in the bulk and 9,500 lbs/in^2 at the orifice, is being exerted on the plunger of the syringe. No material is ejected.

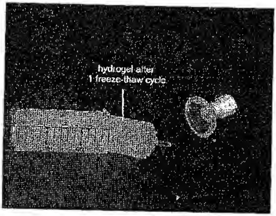

Figure 15: Depicts that the syringe containing the single freeze-thawed hydrogel composed of 15 wt% PVA in deionized water was cut open, and the hydrogel was partially removed.

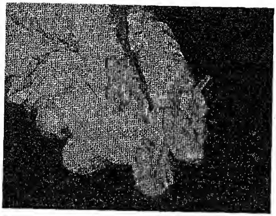

Figure 16: Illustrates the freeze-thawed hydrogel after removal from the sectioned syringe. The hydrogel is a solid material, resistant to mechanical deformation and is not an injectable hydrogel.

Above comparative experiments and the results (Figures 10-16) also demonstrate that the hydrogels produced by freeze-thaw process are not injectable.

4. In summary, the hydrogels disclosed in the cited references are not injectable and the methods disclosed therein also do not produce "injectable hydrogel." Hence, the "injectable hydrogel" recited in claims 113-119 is characteristically, physically as well as chemically, different from the hydrogels disclosed in any of the references cited by the examiner. Therefore, it is concluded that the instantly claimed "injectable hydrogel" is not expressly or inherently disclosed in any of the cited references.

5. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

3/2/2007

Date

Stephen Spiegelberg, Ph. D.